Lipid Biosynthesis

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Why do we care about lipids?

• ~80% of European population overweight
• ~ 1/3 obese

=130 million obese adults in EU
6% of total health costs
10-13% of deaths in Europe

Contributes to diabetes, coronary heart disease, hypertension, stroke & cancer

Diseases of dyslipidemia are one of the greatest health challenges of the 21st century
Outline

• Lipid overview: synthesis and structure
• Fatty acids
• Eicosanoids
• Break . . . .
• Triacylglycerols
• Phospholipids
• Cholesterol
• Bile acids, enterohepatic circulation
• Summary
What is a lipid?

**Classical definition:**
biological molecule that is soluble in organic solvent, but insoluble in water

**Modern (specific) definition:**
fatty acids and their derivatives, and substances related biosynthetically or functionally to these compounds

**More specific definition:**
Hydrophobic small molecules that originate by carbanion-based condensations of thioesters (fatty acids, polyketides, etc.) and/or by carbocation-based condensations of isoprene units (prenols, sterols, etc)

Vary greatly in structure and function
Some typical lipids

In addition:
cholesterol, cofactors, vitamins, bile acids, hormones, eicosanoids, other signaling molecules, etc........
**Free Fatty Acids**

- **16:0n9**
  - **ACC/FAS**
  - **Elongase**
  - **D9D**
  - **18:1n9**

- **18:0n9**
  - **Elongase**

- **18:2n6**
  - **D6D**
  - **18:3n3**
  - **D6D**
  - **18:4n3**
  - **D5D**
  - **20:3n6**
  - **20:4n3**
  - **24:5n3**
  - **24:6n3**
  - **18:3n6**
  - **20:3n6**
  - **20:4n3**
  - **24:6n3**

**Elongase**

**β-oxidation**

**Varying Lipid Class**

- **Plasmologens & Ether phospholipids**
- **Sphingomyelins**
- **Lyso-PC**
- **PE**
- **PS**
- **PI**
- **TGs**
- **DGs**
- **MGs**

**Acyltransferase**

**AT = acyltransferase**

**Peptidase**

**PLA2 = phospholipase A2**

**Lyso-PC AT**

**EPT = ethanolamine-phosphotransferase**

**CEPT1 = choline/EPT-1**

**LCAT, PLA2**

**EPT = ethanolamine-phosphotransferase**

**CEPT1 = choline/EPT-1**

**AT = acyltransferase**

**LCAT = lecithin cholesterol AT**

**ACAT = acyl coenzyme-A:cholesterol transferase**

**LPAT = Lyso-PC AT**

**PEMT = PE methyl transferase**

**PSD = PS decarboxylase**

**PSS = PS synthase**

**CLS = cardiolipin synthase**

**SS = sphingomyelin synthase**

**ACC/FAS = acetyl-CoA carboxylase**

**FAS = fatty acid synthase**

**PC = phosphatidyl choline**

**PE = phosphatidyl ethanolamine**

**PS = phosphatidyl serine**

**PI = phosphatidyl inositol**

**MGs = monoacylglycerols**

**DGs = diacylglycerols**

**TGs = triacylglycerols**

**Glycerol-3-P**

**ACAT**

**Cholesteryl Esters**

**Elongase**

**β-oxidation**
Fatty acids (FA)

- compounds synthesized in nature via condensation of malonyl coenzyme A units by a fatty acid synthase complex
- contain even numbers of carbon atoms in straight chains (commonly C14- C24)
- may be saturated or unsaturated
- can contain variety of substituent groups
Fatty Acids

• Single($\sigma$)-bonded carbon chains with a terminal carboxylic acid:

\[\text{\begin{tikzpicture}[scale=0.2]
\begin{scope}[every node={circle, draw, inner sep=0, minimum size=0.5cm}]
\node (s1) at (0,0) {-};
\node (s2) at (1,0) {-};
\node (s3) at (2,0) {-};
\node (s4) at (3,0) {-};
\node (s5) at (4,0) {-};
\node (s6) at (5,0) {-};
\node (s7) at (6,0) {-};
\node (s8) at (7,0) {-};
\node (s9) at (8,0) {-};
\node (s10) at (9,0) {-};
\node (s11) at (10,0) {-};
\node (s12) at (11,0) {-};
\end{scope}
\draw (-5,0) -- (11,0);
\draw (-4,0) -- (12,0);
\draw (0,-1) -- (0,1);
\node at (11,0) {COOH};
\end{tikzpicture}}\]

• Produced de novo by animals and plants
• Can contain double($\pi$)-bonded carbons which are inserted by desaturases
Unsaturation & shorter chain

- ↓ melting point
- ↑ membrane fluidity (*cis* bond gives the "kink" in the carbon chain)

[Diagram of fatty acid structures showing palmitate and oleate]
Nomenclature

• Fatty acids are sigma-bonded carbon chains with a carboxylic acid functional group
Nomenclature

- Individual fatty acids can be identified by one of two numerical nomenclature systems.

**n-Designation**

Carbon numbering starts from methyl end.

- n-18:0:
  - 18 carbons
  - No double bonds

**Stearic acid**

- 18:0
- No double bonds
Nomenclature

- Individual fatty acids can be identified by one of two numerical nomenclature systems

**Δ-Designation**
Carbon numbering starts from carboxyl group

\[
\begin{align*}
\text{COOH} & \\
17 & 15 & 13 & 11 & 9 & 7 & 5 & 3 & 1 \\
18 & 16 & 14 & 12 & 10 & 8 & 6 & 4 & 2
\end{align*}
\]

stearic acid
18:0
Nomenclature

- Standard nomenclature (arachidonic acid):

20:4 $\Delta_{5,8,11,14}$

- $n$-Designation:
  - 20:4 n6

- $\Delta$-Designation:
  - $\Delta_{5,8,11,14}$

- Carb, Num, Position of double bonds

- $\omega$: 6
Desaturation of Fatty Acids
complex of 3 membrane proteins in E.R.

series of desaturase enzymes creates position-specific double bonds

stearic acid – 18:0

oleic acid – 18:1, cis
Fatty Acid Metabolism

• The first desaturation of a saturated fatty acid is always at the $\Delta 9$ position.
Fatty Acid Metabolism

- Plants can also desaturate at the Δ12
Fatty Acid Metabolism

- Plants can also desaturate at the $\Delta 12$ and the $\Delta 15$ carbon
Fatty Acid Metabolism

- Animals desaturate plant-derived polyunsaturated fatty acids (PUFAs) at the Δ6 carbon.
To add another double bond, animals must first elongate the fatty acid.
Fatty Acid Metabolism

- Animals can then add a $\Delta 5$ double bond
Fatty Acid Metabolism

- To make docosahexaenoic acid (DHA, 22:6n3) animals must further elongate the acyl chain to 22 carbons.
Fatty Acid Metabolism

- Another double bond is inserted at the Δ4 position

Diagram:
- Δ15
- Δ12
- Δ9
- Δ9
- Δ6
- Δ5
- Δ4?
- 22:5n3 docosapentaenoic acid
- COOH
Fatty Acid Metabolism

- BUT THERE IS NO Δ4 DESATURASE
Fatty Acid Metabolism

- To make DHA (22:6n3) the fatty acid must first be elongated again to a 24 carbon chain

![Diagram of fatty acid metabolism]

- Δ9
- Δ12
- Δ15
- Δ5
- Δ6
- Elongase
- tetracosapentaenoic acid
- 24:5n3
- COOH
Fatty Acid Metabolism

• Then the chain can be acted upon again by the Δ6 desaturase yielding 24:6n3
The last step in DHA synthesis is a 2-carbon chain shortening by peroxisomal β-oxidation.

docosahexaenoic acid (22:6n3)
Fatty Acid Metabolism

- Fatty acids with double bonds on the methylene side of an original $\Delta 9$ double bond (n3 and n6 bonds) are of plant origin.
Animals then modify these polyunsaturated fatty acids utilizing their own distinct set of desaturases.
Fatty Acid Metabolism

• Why two designations?
  – One is useful to describe biochemical reactions
  – One is useful to track families of fatty acids in nutrition
Biochemical Reactions

• Desaturases and elongases act from the carboxy-terminus of the fatty acid

• Therefore, the Δ-designation is useful to describe the biochemistry of fatty acid metabolism

Double bond inserted 9 carbons from COOH

\[ \Delta^9 \]
Nutrition

• The n-designation is useful as it allows nutritionists to link diet with tissue fatty acid composition

Linoleic acid (18:2n6)

Δ12  Δ9  Cannot change n6

COOH

n6
Omega fatty acids (ω)

- Nomenclature based upon position of the first double bond relative to the carbon chain terminal methyl
- Omega-3 fatty acids cannot be synthesized de novo by humans, obtained from fish

\[
\text{docosahexaenoic acid (DHA)}
\]

- Omega-6 fatty acids are obtained from diet (grains, etc) and can be synthesized

\[
\text{arachidonic acid (AA)}
\]
Fatty acid modification

- Activated FFA (acyl-CoA)
- Elongation
- $\beta$-oxidation
- Desaturation
  - up to C9 in animals
  - $>$C9 occurs only in plants
Essential FA Metabolism

\[ \text{E/Δ6/β-ox} \]

- \[ 22:5n6 \]
- \[ 22:6n3 \]
- \[ 22:2n6 \]
- \[ 22:4n6 \]
- \[ 22:5n3 \]
- \[ 22:3n3 \]

\[ \Delta 5 \]

- \[ 20:4n6 \]
- \[ 20:5n3 \]
- \[ 20:3n6 \]
- \[ 20:3n6 \]
- \[ 20:4n3 \]
- \[ 20:3n3 \]

\[ \Delta 6 \]

- \[ 18:3n6 \]
- \[ 18:4n3 \]
- \[ 18:2n6 \]
- \[ 18:3n3 \]
De Novo Metabolism

Elongase

24:0 24:1
22:0 22:1
20:0 20:1 18:1
18:0

18:1n9 16:1n7

Δ9 Desaturase

Δ5

18:2 20:2
20:3n9

Δ6
Trans-fat contains “trans” vs. “cis” bond

- Saturated
- cis double bond
- trans double bond

Oleic acid – C18, cis
Melting point = 13°C

Elaidic acid – C18, trans
Melting point = 45°C
<table>
<thead>
<tr>
<th>Number of carbons</th>
<th>Number of double bonds</th>
<th>Common name</th>
<th>Systematic name</th>
<th>Formula</th>
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<td>Laurate</td>
<td>n-Dodecanoate</td>
<td>CH₃(CH₂)₁₀COO⁻</td>
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<tr>
<td>14</td>
<td>0</td>
<td>Myristate</td>
<td>n-Tetradecanoate</td>
<td>CH₃(CH₂)₁₂COO⁻</td>
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<td>16</td>
<td>0</td>
<td>Palmitate</td>
<td>n-Hexadecanoate</td>
<td>CH₃(CH₂)₁₄COO⁻</td>
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<td>18</td>
<td>0</td>
<td>Stearate</td>
<td>n-Octadecanoate</td>
<td>CH₃(CH₂)₁₆COO⁻</td>
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<tr>
<td>20</td>
<td>0</td>
<td>Arachidate</td>
<td>n-Eicosanoate</td>
<td>CH₃(CH₂)₁₈COO⁻</td>
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<tr>
<td>22</td>
<td>0</td>
<td>Behenate</td>
<td>n-Docosanoate</td>
<td>CH₃(CH₂)₂₀COO⁻</td>
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<td>24</td>
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<td>Lignocerate</td>
<td>n-Tetracosanoate</td>
<td>CH₃(CH₂)₂₂COO⁻</td>
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<tr>
<td>16</td>
<td>1</td>
<td>Palmitoleate</td>
<td>cis-Δ⁹-Hexadecenoate</td>
<td>CH₃(CH₂)₁₅CH=CH(CH₂)₂COO⁻</td>
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<tr>
<td>18</td>
<td>1</td>
<td>Oleate</td>
<td>cis-Δ⁹- Octadecenoate</td>
<td>CH₃(CH₂)₁₅CH=CH(CH₂)₂COO⁻</td>
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<td>18</td>
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<td>Linoleate</td>
<td>cis,cis-Δ⁹,Δ¹²-Octadecadienoate</td>
<td>CH₃(CH₂)₁₄(CH=CHCH₂)₂(CH)₆COO⁻</td>
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<tr>
<td>18</td>
<td>3</td>
<td>Linolenate</td>
<td>all-cis-Δ⁹,Δ¹₂,Δ¹⁵-Octadecatrienoate</td>
<td>CH₃CH₂(CH=CHCH₂)₃(CH₂)₆COO⁻</td>
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<tr>
<td>20</td>
<td>4</td>
<td>Arachidonate</td>
<td>all-cis Δ⁵,Δ⁸,Δ₁¹,-Δ¹⁴ Eicosatetraenoate</td>
<td>CH₃(CH₂)₄(CH=CHCH₂)₄(CH₂)₂COO⁻</td>
</tr>
</tbody>
</table>

Ex) Linoleate, linoleic acid  \(18:2\text{n}6\)

cis,cis-Δ⁹,Δ¹² —octadecatrienoate

an \(\omega\)-6 fatty acid
Fatty acid biosynthesis

• **Where?** In the cytoplasm in: liver, adipose and mammary glands

• **How?** Stepwise incorporation of 2 carbon atoms from Acetyl-CoA

• **Cost?** both ATP and NADPH
Overall equation for synthesis of 16:0 (palmitate, hexadecanoate)

$$8 \text{ Ac-CoA} + 7\text{ATP} + 14 \text{ NADPH} + 14\text{H}^+ \rightarrow 16:0 + 8 \text{ CoA} + 7\text{ADP} + 7\text{P}_i + 14\text{NADP}^+ + 6\text{H}_2\text{O}$$

Palmitate
Fatty acid synthase system

Domain 1:
AT acetyl transferase
MT malonyl transferase
CE condensing enzyme
(=β-ketoacyl synthase, KS)

Domain 2:
DH dehydratase
ER enoyl reductase
KR β-ketoacyl reductase
ACP acyl carrier protein

Domain 3:
TE thioesterase
"activated 2-carbon donor" committed step in FA synthesis
Coenzyme A (CoA-SH)

Reactive group

β-Mercapto-ethylamine unit

Pantothenate unit

Acyl CoA

Acetyl CoA
Acetyl-CoA-carboxylase (ACC) is the committed step in FA synthesis.

Acetyl-CoA + ATP + HCO₃⁻ → Malonyl-CoA + ADP + Pi + H⁺
Elongation phase of FA synthesis

Acetyl transacylase
Acetyl CoA + ACP ⇌ acetyl ACP + CoA

Malonyl transacylase
Malonyl CoA + ACP ⇌ malonyl ACP + CoA
ACP – acyl carrier protein

Acyl carrier protein

Coenzyme A

Single polypeptide chain of 77 residues
Fatty acid synthase reaction sequence

2 carbons + 3 carbons + 4 carbons = 7 rounds gives: 16:0, palmitate
"fatty acid machine"
AT = acetyl transferase
MT = malonyl transferase
KS = β-ketoacyl synthase, (CE condensing enzyme)
HD = dehydratase
ER = enoyl reductase
KR = β-ketoacyl reductase
ACP = acyl carrier protein
AT = acetyl transferase
MT = malonyl transferase
KS = β-ketoacyl synthase,
   (CE condensing enzyme)
HD = dehydratase
ER = enoyl reductase
KR = β-ketoacyl reductase
ACP = acyl carrier protein
Ex) The complete reaction for synthesis of 16:0

\[ 8 \text{ Ac-CoA} + 7 \text{ ATP} + 14 \text{ NADPH} + 14\text{H}^+ \rightarrow 16:0 + 8 \text{ CoA} + 7\text{ADP} + 7\text{P}_i + 14\text{NADP}^+ + 6\text{H}_2\text{O} \]

\[ = 1 \text{ Ac-CoA} + 7 \text{ Mal-CoA} \]

---

Palmitate
(ionized form of palmitic acid)
Transfer of Acetyl-CoA to the cytosol

→ FA synthesized in cytoplasm, acetyl CoA formed from pyruvate in mitochondria

\[
\text{Citrate} + \text{ATP} + \text{CoA} + \text{H}_2\text{O} \rightarrow \text{acetyl CoA} + \text{ADP} + \text{P}_i + \text{oxaloacetate}
\]
2 Ways to Generate NADPH

1. Malic enzyme  
   (NADP⁺-linked malate enzyme)

2. HMP-shunt  
   (hexose monophosphate)

occurs exclusively in the cytoplasm = accounts for 60% of NADPH
Fatty acid synthesis requires the integration of multiple metabolic pathways.
EICOSANOIDs
AA is metabolized to inflammatory mediators

Many current anti-inflammatory & pain medicines inhibit some portion of the AA pathway
Eicosanoid hormones are derived from PUFAs

- Arachidonic acid (20:4n6) is major precursor of multiple signal molecules:
  prostaglandins (PG), prostacyclins, thromboxanes (TX) and leukotrienes (LT)
- PGs = 20 carbon fatty acids containing a 5-carbon ring
- PGs stimulate inflammation, regulate blood flow, control ion transport, modulate synaptic transmission & induce sleep

![Chemical structure of PGH2]
Importance of eicosanoids

- Nobel Prize in 1982 for discovery of PG biological role and 1990 for PG synthesis
- PGs are found in almost all tissues & organs
- Ex of PG antagonists:
  - NSAIDs (inhibit COX → aspirin, ibuprofen)
  - corticosteroids (inhibit phospholipase A2 production)
- TXs are vasoconstrictors & hypertensive agent
  - role in thrombosis (clot in blood vessel)
- LTs & cysteinyL-LTs important in inflammation
  - asthma, psoriasis, anaphylaxis & atherosclerosis
# Eicosanoid-based medicines

<table>
<thead>
<tr>
<th>Type</th>
<th>Medical condition</th>
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<tbody>
<tr>
<td>PGI&lt;sub&gt;1&lt;/sub&gt; analog</td>
<td>Pulmonary hypertension, avoiding reperfusion injury</td>
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<tr>
<td>PG analog</td>
<td>Glaucoma, ocular hypertension</td>
</tr>
<tr>
<td>PG analog</td>
<td>Labor induction</td>
</tr>
<tr>
<td>PGE&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Labor induction</td>
</tr>
<tr>
<td>PGI&lt;sub&gt;2&lt;/sub&gt; analog</td>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>PGE&lt;sub&gt;1&lt;/sub&gt; analog</td>
<td>Stomach ulcers, labor induction</td>
</tr>
<tr>
<td>LT receptor antagonist</td>
<td>Asthma, seasonal allergies</td>
</tr>
<tr>
<td>PGI analog</td>
<td>Pulmonary hypertension</td>
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</table>
PGH$_2$ promotes inflammation and modulates gastric acid secretion.
PGH$_2$ synthase-1 is held in the membrane by $\alpha$-helices coated with hydrophobic side chains. AA is hydrophobic and is funneled thru protein channel.
Ser 530

Hydrophobic channel

PGH$_2$ synthase-1

Serine

Aspirin (Acetylsalicylic acid)

Ser$_{530}$-O-CH$_3$
The Arachidonic Acid Cascade Contains 3 Profiles

Cyclooxygenase-Dependent Metabolism

Lipoxygenase-Dependent Metabolism

Cytochrome P450-Dependent Metabolism

Inflammatory
Proliferative
Vasoconstrictive
Coagulation

Modulation of Glucose Metabolism
Biosynthesis of membrane lipids and steroids
Triacylglycerol (TAG) = ester of glycerol + 3 FA
Phospholipids (PL) major class of membrane lipids

Glycerophospholipid constructed of 4 components

hydrophobic

hydrophilic

Membrane
1st step in synthesis of phospholipids (PLs) and triacylglycerols (TAGs) is the synthesis of phosphatidate.

Phosphatidate (Diacylglycerol 3-phosphate)
Phosphatidate is built from L-glycerol-3-phosphate and activated fatty acids.
TAG synthesis proceeds via DAG
Triacylglycerols (TAG)

- Stored energy in fat cells
  - adipose cells
- More energy/gram than carbohydrates
  - 9 kcal/g compared to 4 kcal/g
  - stored in anhydrous form (carbs 2g H₂O/g)

=> fat has 6.75x > energy than hydrated glycogen
TAG cycle

Adipose tissue
- Triacylglycerol
- Glycerol 3-phosphate
- Lipoprotein lipase
- Glycerol

Blood
- Glycerol
- Fatty acid
- Fuel for tissues

Liver
- Triacylglycerol
- Fatty acid
- Glycerol 3-phosphate
Glycerophospholipids (phosphoglycerides)

- glycerol-based PLs – main component of biological membranes
<table>
<thead>
<tr>
<th>Name of glycerophospholipid</th>
<th>Name of X</th>
<th>Formula of X</th>
<th>Net charge (at pH 7)</th>
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<tr>
<td>PA</td>
<td>Phosphatidic acid</td>
<td>$-\text{H}$</td>
<td>-1</td>
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<tr>
<td>PE</td>
<td>Phosphatidylethanolamine</td>
<td>$\text{CH}_2-\text{CH}_2-\text{NH}_3$</td>
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<tr>
<td>PC</td>
<td>Phosphatidylcholine</td>
<td>$\text{CH}_2-\text{CH}_2-\text{N(CH}_3)_3$</td>
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<tr>
<td>PS</td>
<td>Phosphatidylserine</td>
<td>$\text{CH}_2-\text{CH}_2-\text{COO}^- \text{NH}_3$</td>
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<td>PG</td>
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<tr>
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<td>Phosphatidylinositol 4,5-bisphosphate</td>
<td>$\text{myo-Inositol 4,5-bisphosphate}$</td>
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<tr>
<td>CL</td>
<td>Cardiolipin</td>
<td>$\text{CH}_2-\text{CH}_2-\text{O-PO-CH}_2-\text{CO-CH}_2$</td>
<td>-2</td>
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</tbody>
</table>
Biological role of PLs

- PC most common lipid in mammals
- PS is 10% of total PLs in mammals
- CL located in inner mitochondrial membrane (role in oxidative phosphorylation)
- Ampipathic = possesses both hydrophilic and hydrophobic properties
PL synthesis requires an activated intermediate

**Strategy 1**
Alcohol activation of CDP

**Strategy 2**
DAG activation of CDP

CDP = cytidine diphosphate
Strategy 1
PL synthesis from activated alcohol

CDP=cytidine diphosphate
Strategy 2

PL synthesis from activated DAG

CTP=cytidine triphosphate
CDP=cytidine diphosphate
CMP=cytidine monophosphate
Glycerophospholipid synthesis

PE and PC: **Strategy 1**
PI, PG, cardiolipin (CL): **Strategy 2**

PS, PE, PC are “coupled”
PS from PE or PC
PC from PE (+ 3 adoMet)
Sphingolipids contain sphingosine backbone (not glycerol)

Sphingosine

Fatty acid
PO₄ Choline

Glycerol
Fatty acid
Fatty acid
PO₄ Alcohol

Glycerophospholipid

Sphingomyelin

Phosphatidylinositol

Membrane lipid = concentration ↑ in central nervous system
Pathway integration for TAG and PL synthesis
phosphatidate is produced from multiple pathways
and is further incorporated into TAGs or PLs

*For phospholipid synthesis, either phosphatidate or the alcohol must be activated by reaction with an NTP*
Cholesterol biosynthesis modulates fluidity in animal membranes and is precursor of steroid hormones.
where **isoprene** is the key intermediate
1. Condensation of 3 Ac-CoA to mevalonate

2. Conversion of mevalonate to activated isoprene (3-isopentenyl pyrophosphate)

3. Condensation of 6 activated isoprene units to squalene

4. Cyclization

HO

Cholesterol
Step 1: Condensation of 3 Ac-CoA to mevalonate (6 carbons)
Step 2: Conversion of mevalonate to activated isoprenes (5 carbons)
Step 3: Cond. of isoprene-units to squalene (linear, 30 carbons)

5 + 5

= 10

+ 5

= 15

+ 15

= 30
Step 4: Cyclization (4 rings)

Squalene → Squalene epoxide → Protosterol cation

19 steps

Cholesterol → Lanosterol
All 27 carbons in cholesterol are derived from Ac-CoA
1. Condensation of 3 Ac-CoA to mevalonate limiting step!!

2. Conversion of mevalonate to activated isoprene (3-isopentenyl pyrophosphate)

3. Condensation of 6 activated isoprene units to squalene

4. Cyclization
Regulation of HMG-CoA-reductase
(integral membrane protein in ER)

1. Feedback – cholesterol stimulates proteolysis
2. Hormonal – inactivated by phosphorylation, activated by dephosphorylation
3. Transcription - via SREBP (rate of synthesis) sterol regulatory element binding protein
4. Therapeutics - mevalonate analogs competitive inhibitor – statins lovastatin, atorvastatin - Lipitor
SREBP pathway = sterol regulatory binding element protein
Cholesterol is a precursor to bile salts (and to steroid hormones and vitamin D)
Enterohepatic circulation

circulation of bile from the liver, to the small intestine where it aids in fat digestion

hepatocytes metabolize cholesterol to lipid-soluble bile acids → bile salts
conjugated to glycine or taurine

the enterohepatic circulation of bile acids may be disrupted as a way to lower cholesterol
Free Fatty Acids

- Acetyl-CoA
- ACC/FAS
- 16:0n9
- Elongase
- 18:0n9
- D9D
- 18:1n9

- 18:2n6
- D6D
- 18:3n3
- Elongase
- 18:4n3
- D5D
- 20:4n6
- 20:5n3
- Elongase
- 22:5n3

- 22:6n3
- β-oxidation

Varying Lipid Class

- Plasmologens & Ether phospholipids
- Sphingomyelins
- Lyso-PC
- Acetyl-CoA carboxylase (ACC/FAS)
- Elongase
- D9D
- D6D
- Elongase
- β-oxidation

- TGs
- AT
- Cardiolipin
- PE
- PSS2
- PSS1
- PE methyl transferase (PEMT)
- Cardiolipin synthase (CLS)
- Cholesterol esters
- Cardiolipin

- PSS = PS synthase
- PSD = PS decarboxylase
- PSS2 = PS synthase
- PE = phosphatidyl ethanolamine
- PI = phosphatidyl inositol
- PS = phosphatidyl serine
- PC = phosphatidyl choline
- MGs = monoacylglycerols
- DGs = diacylglycerols
- TGs = triacylglycerols

AT = acyltransferase
ACAT = acyl coenzyme-A:cholesterol transferase
LPAT = Lyso-PC AT
PEMT = PE methyl transferase
PLA2 = phospholipase A2
CPT = carnitine palmitoyltransferase
EPT = ethanolamine-phosphotransferase
CEPT1 = choline/EPT-1
CL = cholesteryl ester
AT = acyltransferase
LCAT = lecinthin cholesterol AT
FAS = fatty acid synthase
ACAT = acyl coenzyme-A:cholesterol transferase
What is a lipid?

**Classical definition:**
biological molecule that is soluble in organic solvent, but insoluble in water

**Modern (specific) definition:**
fatty acids and their derivatives, and substances related biosynthetically or functionally to these compounds

**More specific definition:**
Hydrophobic small molecules that originate by carbanion-based condensations of thioesters (fatty acids, polyketides, etc.) and/or by carbocation-based condensations of isoprene units (prenols, sterols, etc)
Lipid Biosynthesis - summary

- **Lipids overview** classification, structure, synthesis
- **Fatty acids** in liver (fat) and cytosol; Mal-CoA; multifunctional enzyme; modified in ER
- **Eicosanoids** important signaling molecules; play roles in pain and inflammation
- **Triacylglycerols** in liver, fat, and intestine; energy storage; phosphatidate; dynamic equilibrium
- **Phospholipids** in almost all cells; phosphatidate, 2 strategies for synthesis, membrane components
- **Cholesterol** in all cells; mostly liver, 4 steps, from Ac-CoA via isoprene, HMG-CoA reductase
- **Bile acids** important in fat digestion, enterohepatic circulation

Whew…….
- http://www.cyberlipid.org/
- http://www.lipidlibrary.co.uk/
- http://www.lipidmaps.org/
- http://www.metabolomics.se/
  - (contains downloadable file of today’s lecture under the section “Courses”)